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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/205,658 | 12/03/1998 | GARY RUVKUN | 00786/351004 | 7404 |

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| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |
| ART UNIT | PAPER NUMBER |
| 1636 | 24 |

DATE MAILED: 06/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/205,658 | Applicant(s) RUVKUN ET AL. |
|---|---|---|
| | Examiner S. Kaushal | Art Unit 1632 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 September 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,8,10-23 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10-23 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## *DETAILED ACTION*

In response to a telephonic interview with Keren Elbing on 05/30/02 the finality of last office action mailed on 03/28/01 is withdrawn and a non-final office action has been issued to address new grounds of rejections below.

*Claims 1-5, 8, 10-~~17~~, 23 and 25-28 were pending and were examined in this office action.*

▶ *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.*

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 12-15, 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession of the claimed invention**.

The scope of invention as claimed encompasses any and all daf-18 nematode homologs and any and all mammalian PTEN genes. At best the specification as filed only discloses C.elegans daf-18 and human PTEN gene (spec. page 108, line 19). The instant specification fails to disclose any daf-18- homolog isolated from any and all nematodes. Similarly, instant specification fails to disclose PTEN-homolog isolated from any and all mammals. There is no

description of mutational sites that exist in nature, and there is no description how the structure of nematode-daf-18 or human-PTEN relates to the structure of any other nematode or mammalian homologs respectively. The art at the time of filing teaches that daf-18 encodes a homolog of the human tumor suppressor PTEN (MMAC1/TEP1), which has 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate (Ogg et al, Mol. Cell 2:887-893, 1998, see abstract). In addition, the mammalian PTEN-like polypeptides include members that would expect to have widely divergent functional properties. The specification only disclosed nucleic and amino acid sequences encoding C.elegans daf-18 and human PTEN polypeptide. The specification fails to disclose nucleic and amino acid sequences encoding daf-18-like and/or PTEN-like protein obtained from any other animal. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In addition possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention Pfaff v. Wells Electronics, Inc 48 USPQ2d 1641, 1646 (1998). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1-5, 8 and 10-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that modulates C.elegans DAF-18 (*in isolated C. elegans cells*) or human PTEN (*in isolated mammalian cells)* expression or activity, does not reasonably provide enablement for a method for identifying a

compound that modulates DAF-18 or PTEN expression or activity, wherein the DAF-18 and PTEN are obtained from any and all nematodes or mammals respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

The instant claims are drawn to a method for identifying compound that modulates nematode Daf-18 expression or activity in a nematode, isolated nematode cell or isolated mammalian cell. The claims are drawn to a method a method for identifying compound that modulates mammalian PTEN expression or activity in a nematode, isolated nematode cell or isolated mammalian cell. The specification as filed only discloses C.elegans daf-18 and human PTEN genes. The instant specification fails to disclose any daf-18- homolog isolated from any and all nematodes (spec. page 108, line 19). Similarly, instant specification fails to disclose PTEN-homolog isolated from any and all mammals (spec. page 108, line 19). There is no description of mutational sites that exist in nature, and there is no description how the structure of C.elegans-daf-18 or human-PTEN relates to the structure of any other neamtode or mammalian homologs. The art at the time of filing teaches that daf-18 encodes a homolog of the human tumor suppressor PTEN (MMAC1/TEP1), which has 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate (Ogg et al, Mol. Cell 2:887-893, 1998, see abstract). Scope of invention as claimed encompasses daf-18 and PTEN homolog obtained from any and all nematodes and mammals respectively. Furthermore, the genetic interaction among various DAF genes and/or gene products is complex and is only well studied in C.elegans (Larsan et al, Genetics 139:1567-83, 1995; ref of record). The specification fails to provide any guidance that the structure of C.elegans-daf-18 or human-PTEN relates to the structure of any other nematode mammalian homologs. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. It is unclear how one skill in the art would use the invention as claimed when the specification fails to provide

guidance that any and all nematodes daf-18 and any and all mammalian PTEN are identical in structure and have similar functions. Therefore, it is concluded that applicant has not presented enablement commensurate in scope with the claims.

Claims 23 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic C. elegans whose cells contain a transgene encoding human PTEN polypeptide, does not reasonably provide enablement for any and all nematodes whose cells contain a transgene encoding any and all mammalian PTEN polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

The invention as claimed encompass a transgenic nematode whose cell contain a transgene encoding mammalian PTEN, wherein the nematode caries a mutation in its endogenous daf-18 gene. The specification fails to disclose a transgenic nematode whose cells contain a transgene encoding mammalian PTEN. At best Dr. Ruvkun's declaration filed on Paper No. 14 (07/14/00) only disclosed a transgenic C.elegans whose cells contain a transgene encoding human PTEN polypeptide (declaration, page 2, para.6). The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425). In instant case, the genetic interaction among various DAF genes and/or gene products is complex and is only well studied in C.elegans (Larsan et al,

Genetics 139:1567-83, 1995; ref of record). The specification fails to provide any guidance that the structure of C.elegans-daf-18 or human-PTEN relates to the structure of any other neamtode or mammalian homologs. The lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Wall RJ Theriogenology 45:57-68, 1996, page 61-62, ref of record). Cis acting elements of one species may interact with different transactivating factors in other species. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235). Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, 548). Thus, in view of lack of specific guidance in the specification, the skilled artesian at the time of filing would be unable to make and use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making of any and all transgenic nematodes encoding any and all mammalian PTEN genes.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The rejection of instant claim could be overcome through an amendment by inserting -- with a candidate compound to determine the effect of said compound on daf-18 expression or activity wherein -- before "an alteration in daf-18" in line 6 of claim 1(b).

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The rejection of instant claim could be overcome through an amendment by inserting -- with a candidate compound to determine the effect of said compound on daf-18 expression or activity wherein -- before "an alteration in PTEN" in line 8 of claim 1(c).

***Notice To Comply***

*Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application (see MPEP 2422.03).

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and

that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

The instant specification fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures. For example, the specification discloses nucleotide and/or amino acid sequences on pages 83, 97-100 and 178-187. However, these sequences are not identified by any sequence identifiers (SEQ ID NO). In addition, it is unclear whether these sequences are disclosed in the sequence listing as submitted with the instant specification.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem Yucel can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

*S. Kaushal*
Patent examiner

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER